National PBM Drug Monograph
Eszopiclone (Lunesta™)
April 2005
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

- **Indications/usage:** Eszopiclone (Lunesta™) is a non-benzodiazepine sedative hypnotic agent. It received FDA approval on December 15, 2004 for the treatment of insomnia in adult patients ≥ 18 years of age.
- **Efficacy:** Several double-blind, placebo-controlled studies have demonstrated that eszopiclone is safe and effective in the treatment of transient insomnia (symptoms lasting several days or weeks in duration) and chronic insomnia (symptoms occurring every night or at least 3 times per week for at least 4 weeks) in adult patients. In controlled outpatient and sleep laboratory studies, eszopiclone has been shown to improve sleep onset (time required to initially fall asleep), sleep maintenance (staying asleep) and total amount of time spent sleeping (sleep duration). Patient-reported improvements in the quality of sleep and assessments to determine next-day measures (daytime alertness, physical well being, and daytime ability to function) were observed. No tolerance or significant rebound insomnia has been observed with eszopiclone in the available trials. One of two double-blind, placebo-controlled study conducted specifically in the elderly (65-86 years of age) has been published at the time of this review.
- **Safety:** The most common adverse events associated with eszopiclone include headache (17% vs. 13% on placebo), somnolence (10% vs. 3% on placebo) and unpleasant taste (34% vs. 3% on placebo).
- Eszopiclone is metabolized by the CYP 450 liver enzymes; substrate for 3A4 and 2E1. It is recommended that the dose of eszopiclone be reduced in patients who are administered potent inhibitors of CYP3A4 (e.g., itraconazaole, clarithromycin, erythromycin, nefazodone, troleandomycin, ritonavir, nelfinavir). An increased bioavailability was seen when eszopiclone was co-administered with ketoconazole. No clinically significant drug-drug interactions have been seen in evaluations performed with warfarin, digoxin, lorazepam, paroxetine.
- **Laboratory monitoring:** There are no specific laboratory tests recommended.
- **Dose:** The dose of eszopiclone should be individualized. Eszopiclone should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep. In the elderly, with a primary complaint of difficulty falling asleep, the recommended starting dose is 1 mg immediately before bedtime. For elderly patients whose primary complaint is difficulty staying asleep, the recommended dose is 2 mg immediately before bedtime. For most non-elderly adults, the recommended starting dose is 2 mg immediately before bedtime. The dose can be initiated at or raised to 3mg if clinically indicated, since 3mg is more effective for sleep maintenance.
- **Cost:** Eszopiclone is available as a 1mg, 2mg or 3mg film-coated tablet. The FSS cost for each dose size is $2.22.

Introduction

Insomnia is characterized by difficulty maintaining or initiating sleep, early morning awakenings and/or non-restorative sleep coupled with distress/impairment in next-day activities. It is a significant health concern that is associated with psychiatric, physical, social and economic morbidity.[1-3] Self-reported sleep difficulties range from 10-40% among community residents and primary care patients.[4] As much as 10-15% of adults report persistent sleep problems; [5] rates of sleep problems among women and older adults are even higher.[5-6]

Eszopiclone (Lunesta™) received FDA approval on December 15, 2004 for the treatment of insomnia in adult patients ≥ 18 years of age. Eszopiclone is an oral nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. Eszopiclone is the (S)-isomer of the racemic zopiclone [(R, S)-zopiclone] which is another hypnotic agent that has been available since 1987 in countries outside the United States. The (S)-isomer is responsible for the hypnotic effects of zopiclone, where as the (R)-isomer has no hypnotic properties.[7] Eszopiclone is classified as a Schedule IV controlled substance.

Pharmacology [8-9]

The precise mechanism of action of eszopiclone as a hypnotic agent is unknown although it is believed to be the result of its interaction with GABA-A receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors resulting in cellular hyperpolarization. These GABA-A receptors, identified by different alpha subtypes are located in a variety of places within the CNS and possess different neurophysiological functions. Currently, 6 known alpha subtypes have been identified. GABA receptors alpha-1 and alpha-3 subtypes are associated with controlling sleep. The sleep-inducing activity of both zopiclone stereoisomers (R,S) was determined through performance of in-vitro studies; the S-isomer displayed considerable activity at both alpha-1 and alpha-3 GABA-receptor subtypes. Binding affinity evaluations have demonstrated that eszopiclone, [(S)-zopiclone], has a 1000x greater binding affinity for GABA-A receptor complexes than R-zopiclone.

Pharmacokinetics Parameters in Adults and Elderly‡ (≥ 65 years of age) [10-11]

Absorption	Protein binding	t½	Metabolism	Excretion	Food effect
1 hour	52-59%	6* hours 9**† hours	CYP 3A4 CYP 2E1 (Primarily by oxidation and demethylation, no hypnotically active metabolites	75% urine as inactive metabolites	No change in $t_{1/2}$ life; absorption delayed by 1-2 hrs, which may reduce the speed of sleep onset

* Average of 1, 3, 6mg doses; ** average of 1, 2, 3, and 5mg doses

Absorption: Eszopiclone is rapidly absorbed following oral administration with T_{max} occurring at 1 hour post-dose in healthy subjects.

Distribution: Racemic zopiclone has an absolute volume of distribution of approximately 90L. Eszopiclone would be expected to exhibit similar distributive properties. Eszopiclone is weakly bound to plasma protein (52-59%).

Metabolism: Eszopiclone is a substrate for the CYP3A4 and CYP2E1 metabolic enzymes. Eszopiclone has two primary metabolites: (S)-desmethylzopiclone and (N)-oxide-zopiclone. These metabolites are reported as not possessing clinically relevant hypnotic activity. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes and therefore, would not be expected to alter the metabolism of other drugs.

Elimination: Renal excretion is the principal route of elimination of the metabolites. Approximately 75% of the dose is excreted in urine primarily as metabolites. Less than 10% of the dose is excreted in the urine as unchanged drug. After oral administration, eszopiclone is eliminated with a mean $t_{1/2}$ life of approximately 6 hours in healthy (non-elderly) adults. In the elderly, (≥ 65 years old) elimination is prolonged ($t_{1/2}$ life approximately 9 hours).

Effect of food: In healthy adults, administration of a 3 mg dose of eszopiclone after a high-fat meal resulted in no change in the AUC, a reduction in mean C_{max} of 21% and delayed t_{max} by ~1 hour. The half-life remained unchanged but sleep onset may be reduced if it is taken with or immediately following a high-fat/heavy meal.

Gender/Race: The pharmacokinetics of eszopiclone in men and women are similar. The manufacture reported that the analysis of the pharmacokinetic data for all races participating in Phase I studies of eszopiclone appeared similar.

Patients ≥ 65 years old: Compared to nonelderly adults, a 41% increase in the AUC and a prolonged elimination ($t_{1/2}$ life) of approximately 9 hours was observed in subjects 65 years and older. The C_{max} was unchanged.

FDA Approved Indication[10]

Eszopiclone is FDA approved for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, eszopiclone administered at bedtime decreased sleep latency and improved sleep maintenance. Eszopiclone has been utilized for the treatment of transient and chronic insomnia in adults.

Current VA National Formulary Alternatives

Drugs Commonly used to Treat Insomnia	Comments
Antihistamine	
diphenhydramine	Anticholinergic side effects
Antidepressants	
trazodone	Not FDA approved for the treatment of insomnia
Benzodiazepines	
temazepam	Onset 45-60 minutes; 3-25 hours half-life
Other, Non-barbiturate	
Chloral Hydrate	Loses effectiveness of inducing and maintaining sleep after 2 weeks of use; 7-10 hours half-life

Dosage and Administration[10]

General Recommendations: Eszopiclone should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep.

Recommendations for Elderly and /or Debilitated Patients: The recommended starting dose is 1mg.

Recommendations for Patients with Concomitant Illness:

Severe hepatic impairment: Dose should not be increased above 2mg in patients with severe hepatic impairment per package insert. It is recommended that the dose be reduced to 1mg in patients with severe hepatic impairment. No dose adjustment appears necessary for mild-to-moderate hepatic impairment.

Any degree of renal impairment: No dose adjustment appears necessary.

Use in patients with depression: Any sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression.

Efficacy

Efficacy Measures

Various sleep efficacy endpoints utilized in trials are depicted and defined in Table 1.

Table 1: Definitions of Efficacy Assessments

Efficacy Endpoints	Definition	Terms used to Evaluate and Assess Efficacy Endpoints
Sleep onset	Time required to initially fall asleep	● Sleep latency (via patient-reported, subjective assessments) ● Latency to persistent sleep (LPS)-an objective Polysomnographic (PSG) assessment
Sleep Maintenance	Ability to sustain sleep throughout the night also referred to as sleep continuity	● Wake time after sleep onset (WASO)-total amount of time spent awake after sleep onset

		● Number of awakenings (objectively assessed as the return to the PSG-define awake state or subjectively reported by the patients rousing from sleep)
Sleep Duration	Total amount of time spent sleeping	● Total sleep time (TST) and sleep efficiency (ratio of total time asleep over a fixed 8 hr opportunity period (in an 8-hr PSG study) x 100, expressed as a percentage)
Next-Day Measures	Sense of well-being, alertness, ability to concentrate, ability to function, morning sleepiness, and number and duration of daytime naps	●Patient-reported vía visual analogue scale (VAS)

Summary of Efficacy Findings

Transient Insomnia: Rosenberg et al.[12] evaluated the efficacy and safety of eszopiclone in healthy, normal sleeping adult volunteers (n=436, mean age 33 years; range 25-50) with transient insomnia. This study was a randomized, double-blind, placebo-controlled study that investigated the dose response of eszopiclone (range of 1mg to 3.5mg) in a model of transient insomnia. The primary efficacy endpoint was the mean objective latency to persistent sleep (LPS), with objective sleep efficiency as the key secondary measure. The patients treated with eszopiclone had significantly less polysomnography (PSG) latency to persistent sleep (all doses except 1mg; $p \leq 0.0001$), wake time after sleep onset (all doses; $p<0.05$), number of awakenings (3mg and 3.5mg only; $p<0.005$) and greater sleep efficiency (all doses; $p<0.02$) compared with placebo. (See Appendix A for additional details.)

Chronic Insomnia: The efficacy and safety of eszopiclone for chronic insomnia (at least 1 month) have been investigated in five randomized, double-blind, placebo-controlled studies.[10] Three [7, 11, 14] of the five studies are published at the time of this review. The results of the 6-month, open-label extension[13] added to the study conducted by Krystal et al.[7] is currently available as an abstract. Two studies[14-15] using eszopiclone specifically in the elderly were conducted.

Krystal et al.[7] conducted a 6 month double-blind, placebo-controlled study. The primary objective was to evaluate the safety of eszopiclone 3mg in 788 adult patients (mean age 44.1 years; range 21-65) with chronic insomnia. The results of the study demonstrated sustained improvements in various sleep parameters, including sleep induction, latency to persistent sleep, sleep maintenance, total sleep time, quality of sleep and next-day effects with eszopiclone 3mg compared to placebo. No tolerance was seen with eszopiclone for up to 6 months. (See Appendix A for more details.). Roth et al.[13] reported in an abstract that no evidence of tolerance or significant adverse events commonly associated with withdrawal upon discontinuation was seen with eszopiclone during the additional 6 months extension open-label study.

Zammit et al.[11] evaluated the hypnotic efficacy and safety of 2mg and 3mg dosage strengths of eszopiclone compared to placebo in 308 adult patients (mean age 39.8, range 21-64) with primary insomnia. The primary efficacy endpoint was the objective latency to persistent sleep (LPS) measured by polysomnographic (PSG) recordings. Secondary objectives were to determine whether tolerance and rebound insomnia occurs after the abrupt discontinuation of treatment and to evaluate the patient-reported impact of treatment on daily functioning. Both doses of eszopiclone reduced the median LPS (15 minutes with eszopiclone 2mg and 13.1 minutes for eszopiclone 3mg vs. 29 minutes for placebo, $p \leq 0.001$) during the 6 week study. The 3mg dose of eszopiclone significantly decreased objective wake time after sleep onset (WASO) by 33.8 min vs. 44.1 min compared to placebo; $p \leq 0.01$. Both doses of eszopiclone significantly increased objective sleep efficiency compared to placebo. (Refer to Appendix A for more details).

Elderly: Two randomized, double-blind, placebo-controlled studies[14-15] are available. For both studies, the elderly participants were not institutionalized or hospitalized patients.

Scharf et al.[10,14,16] conducted a randomized, double-blind, placebo-controlled study to determine the efficacy and safety of eszopiclone 2mg in patients aged 65-85 years with primary insomnia (defined by DSM-IV criteria). Eligible participants were randomized to placebo or eszopiclone 1mg or 2mg at bedtime for 2 weeks. The efficacy of eszopiclone was measured subjectively (morning and evening questionnaires) using an Interactive Voice Response System. The primary endpoints were subjective sleep latency and subjective total sleep time. Of the 231 randomized patients, 210 (90.9%) completed the study. The study demonstrated that eszopiclone 2mg significantly improved mean sleep latency (50 min for eszopiclone 2mg vs. 85.5 minutes for placebo; p=.0034), mean WASO (58.5 minutes for eszopiclone 2mg vs. 74.1 for placebo; p=.0423), mean total sleep time (372.3 minutes for eszopiclone 2mg vs. 328.2 minutes for

placebo; <0.003) over the double-blind period. Eszopiclone 1mg had a significantly shorter sleep latency compared with placebo over the double-blind period; (p=.012). Eszopiclone 1mg was not significantly different from placebo for total sleep time across the double-blind period. (Refer to Appendix A for more details).

Erman et al.[10, 15-16] conducted a randomized, double-blind, placebo-controlled study to evaluate the efficacy (via PSG and patient reports) and safety of eszopiclone in 265 elderly patients (65-85 years of age) with a DSM-IV diagnosis of primary, chronic insomnia. Results are available in an abstract. Patients received eszopiclone 2mg (n=136) or placebo (n=128) during a 2 week treatment period. The key primary endpoints were objective latency to persistent sleep (LPS) and sleep efficiency, time awake after sleep onset (WASO), and the number of awakenings. Patient-reported data were collected via an interactive voice response system in the morning (to assess sleep parameters) and in the evening (to assess daytime function). Eszopiclone 2mg resulted in a significant reduction in objective LPS ($p<0.0001$) and WASO ($p<0.05$) over the treatment period compared to placebo. Sleep efficiency was increased with eszopiclone compared to placebo, ($p<0.04$). Patient-reported sleep latency ($p<0.0001$), WASO ($p=0.0019$) and total sleep time ($p\leq 0.0001$) were significantly decreased with eszopiclone compared to placebo. The most common adverse event reported was unpleasant taste.

Adverse Events (Safety Data) [10]

Common Adverse Events

Zammit et al.[11] reported the most frequently occurring adverse events (≥ 2% of patients) treated with eszopiclone at doses of 2mg or 3mg in a 6 week, Phase III placebo-controlled study of adults with chronic insomnia were unpleasant taste, headache, and somnolence. The incidence of unpleasant taste in patients taking placebo, eszopiclone 2mg and 3mg occurred in 3%, 17% and 34%, respectively. Headache occurred 13% in patients taking placebo; 21% with eszopiclone 2mg and 17% with eszopiclone 3mg. The incidence of somnolence with placebo, eszopiclone 2mg, 3mg was 3%, 10% and 8% respectively. Refer to Appendix A for more details.

The incidence of the common adverse events from the two combined Phase III placebo-controlled studies[14-15] of eszopiclone 1mg or 2mg in older adults (ages 65-86) is listed in Table 2. The most frequently reported adverse event was unpleasant taste.

Table 2: Incidence (%) of Treatment-Emergent Adverse Events in Two Placebo-Controlled Trials[10, 14-15] in Older Adults (age 65-86)

Adverse Event*	Placebo (n=208)	ESZ** 1mg (n=72)	ESZ** 2mg (n=215)
Accidental injury	1	0	3
Headache	14	15	13
Pain	2	4	5
Diarrhea	2	4	2
Dry Mouth	2	3	7
Dyspepsia	2	6	2
Abnormal dreams	0	3	1
Dizziness	2	1	6
Nervousness	1	0	2
Neuralgia	0	3	0
Pruritus	1	4	1
Unpleasant taste	0	8	12
Urinary Tract infection	0	3	0

* Adverse events occurring in ≥ 2% of patients treated with eszopiclone 1mg or 2mg,
** eszopiclone

Tolerability[10]

Krystal et al.[7] studied the tolerance of eszopiclone in a 6-month, double-blind, placebo-controlled study involving 788 subjects. A difference in patient-reported measures of sleep onset, sleep maintenance, sleep quality, and next-day function compared with placebo in patients with chronic insomnia was apparent during the first week of treatment and was maintained through 6 months of the double-blind treatment, with no evidence of tolerance. Roth et al.[13] reported in an abstract that no evidence of the development of tolerance was observed in the 6 month extension phase.

Drug Abuse and Dependence[10]

Minimal information is available regarding the potential for dependence. The package insert provides information of a study conducted in individuals with known histories of benzodiazepine abuse. Eszopiclone at doses of 6 and 12mg produced "euphoric effects similar to those of diazepam 20mg." It was concluded that at doses ≥ 2-fold higher than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both eszopiclone and diazepam.

For further details on the safety results of eszopiclone in the available clinical trials, refer to Appendix A.

Precautions/Contraindications[8]

It is not known whether eszopiclone is excreted in human milk. Caution should be exercised when eszopiclone is administered to a nursing woman.

Precautions[8]

Timing of Drug Administration: Eszopiclone like all sedatives should be taken immediately before bedtime to avoid short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness while still up and about.

Use in the elderly and or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative hypnotic drugs is a concern in the treatment of elderly and /or debilitated patients.

Use in Patients with Concomitant Illness: Clinical experience/data is limited in patients with concomitant illness. Eszopiclone should be used in caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses. The dose should be reduced to 1 mg in patients with severe hepatic impairment. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment or any degree of renal impairment.

Use in patients with Depression: It is recommended the least amount of drug that is feasible should be prescribed in patients exhibiting signs and symptoms of depression as suicidal tendencies may be present in these patients with this condition.

Contraindications[8]

There are no known contraindications to the use of eszopiclone. Refer to the Precautions section for additional information.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name: eszopiclone

Potential name confusion: testolactone; buspirone; risperidone (oral route); ropinirole; theophylline
Potential Severity: Minor-Moderate
Probability: Infrequent

LA/SA for trade name Lunesta:

Potential name confusion: Menest; Cenestin; Lutera; Congestac; Nestabs
Potential Severity: Minor
Probability: Infrequent

Drug Interactions[8, 10]

Drug-Drug Interactions

- Eszopiclone is metabolized extensively by CYP3A4 and CYP2E1 via oxidation and demethylation. The primary plasma metabolites are (S)-zopiclone-N-oxide which has no significant binding to GABA receptors and (S)-N-desmethyldemthylation which has a substantially lower potency than eszopiclone.
- In-vitro studies did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 in cryoperserved human hepatocytes.

Drugs with a Narrow Therapeutic Index

Digoxin: A single dose of eszopiclone 3mg did not affect the PK of digoxin measured at steady state following dosing of 0.5mg twice daily for one day and 0.25mg daily for the next 6 days.

Warfarin: Eszopiclone 3mg administered daily for 5 days did not affect the pharmacokinetics of (R) or (S)-warfarin, nor were there any changes in the prothrombin time following a single 25 mg oral dose of warfarin.

Coadministration with CNS drugs:

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70g/kg for up to 4 hours after ethanol administration.
Paroxetine: Single doses of eszopiclone 3mg and paroxetine 20mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.
Lorazepam: Single doses of eszopiclone 3mg and lorazepam 2mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.
Olanzapine: When eszopiclone 3mg was coadministered with olanzapine 10mg, a pharmacodynamic interaction was seen on a measure of a psychomotor function (i.e. decrease in the Digit-Symbol Substitution Test (DSST) scores). No alteration in the pharmacokinetics of either drug was observed.

Drugs that Inhibit CYP3A4 (ketoconazole)

Coadministration of eszopiclone 3mg to subjects receiving ketoconazole 400mg (potent inhibitor of CYP3A4) for 5 days resulted in a 2.2 fold increase in AUC exposure to eszopiclone. The C_{max} and $t_{1/2}$ life were increased 1.4 fold and 1.3 fold, respectively. It is recommended that the dose of eszopiclone should be reduced in patients who are administered potent inhibitors of CYP3A4 (e.g., itraconazaole, clarithromycin, erythromycin, nefazodone, troleandomycin, ritonavir, nelfinavir).

Drugs that Induce CYP3A4

Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Drug-Lab Interactions

No lab interactions with eszopiclone are known.

Acquisition Costs*

Table 3: Comparison of the Acquisition Costs for eszopiclone and zolpidem

Drug	Dose	Cost/tablet ($)
Eszopiclone	1mg, 2mg, 3mg (film-coated tablets)	2.22
Zolpidem	5mg tablet	1.27
Zolpidem	10mg tablet	1.57

*Prices obtained 4/05.

Pharmacoeconomic Analysis

A budget-impact model is currently being developed by the company.

Conclusions

Eszopiclone, a non-benzodiazepine sedative hypnotic agent decreases sleep latency and improves sleep maintenance. Eszopiclone has been studied in long-term (6 months) double-blind, randomized controlled trials in the treatment of chronic insomnia including in a 6 month, open-label extension phase (total 12 months). Two studies using eszopiclone specifically in the elderly has been conducted. The most frequently reported adverse effect is unpleasant taste.

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Contact person: Janet H. Dailey, PharmD, Clinical Pharmacy Specialist, VA PBM-SHG

Prepared April 2005; updated June 2005

Appendix A: Clinical Trials

Long-term Treatment of Chronic Insomnia in a Nonelderly Adult Population

<table>
<tr><th>Trial/ Purpose</th><th>Inclusion/Exclusion/Endpoints</th><th>Treatment</th><th>Results</th><th>Adverse Events/Withdrawals</th></tr>
<tr>
<td>Krystal et al.[7] 2003

R, DB, PC, MC (70 centers in US) x 6 months; followed by open-label treatment phase for 6 months as depicted in Roth et al.[13] 2004, (abstract only)

Purpose:

To evaluate the safety and efficacy of eszopiclone 3mg administered nightly to patients with chronic insomnia for 12 months.</td>
<td>Inclusion Criteria:

Patients between 21 and 65 years of age

A DSM IV diagnosis of primary insomnia and reporting a usual total sleep time less than 6.5 hours per night and/or a usual sleep latency of more than 30 minutes each night for at least 1 month prior to screening were eligible for randomization.

Exclusion Criteria:

• DSM-IV Axis I psychiatric diagnosis other than primary insomnia, sexual and gender-identity disorders, or Axis II personality disorders (excluded by medical history)
• history of substance abuse or substance dependence
• consume more than 2 alcoholic beverages per day or more than 14 per week
• use any psychotropic, hypnotic, or other medications known to affect sleep or to be contraindicated for use with hypnotics; or
• use over-the-counter analgesics that contain caffeine or herbal supplements, including products with herbs, melatonin, or St. John’s Wort.

Endpoints: (pt reporting via interactive voice response system (IVRS)
1. sleep latency
2. wake time after sleep onset (WAS0)
3. total sleep time
4. # of awakenings
5. # of nights awakened during the week

Rated per scale 0-10:

6. sleep quality
7 daytime ability to function
8 daytime alertness
9. sense of physical well-being</td>
<td><u>6 month duration</u>

Eszopiclone 3mg at bedtime vs. placebo x 6 months. All patients that completed the double-blind period entered into an open-label extension and received eszopiclone 3mg in the same manner.

Safety-assessment:

Monthly visits for safety and compliance assessment and for medication refills. Additionally, a termination visit occurred 5-7 days later after the last dose of the study medication during which the patient was specifically queried for adverse events that occurred upon drug discontinuation.</td>
<td>Baseline: Mean age 44.1 ± 11 years (range, 21-69); female 63%; Caucasian 79%. There was a small, but significant higher weight (84.5 kg vs. 79.1 kg, p <.0027), and BMI (kg/m^3) (29.5 vs. 27.8; p<.0.0039) at baseline in subjects randomized to eszopiclone compared to placebo. No differences were observed between the baseline and the 2 treatment groups in the 9 sleep and daytime ratings with IVRS.

Table 1. Summary of Efficacy Results in the Intent-to-Treat population*
<table>
<tr><th>Sleep Induction Endpoint</th><th>Placebo (n =195)</th><th>ESZ** 3mg (n=593)</th><th>P value</th></tr>
<tr><td><u>Mean Sleep latency, min (SD),</u>
Baseline
Week 1
1 month
6 months</td><td>
96.1 (94.7)
85.4 (81.1)
71.3 (59.8)
63.1 (57.9)</td><td>
90.6 (79.6)
48.2 (56.4)
44.3 (36.5)
47.0 (50.6)</td><td>
.6137
<.0001
<.0001
<.0001</td></tr>
<tr><td>Sleep Maintenance Endpoints</td><td></td><td></td><td></td></tr>
<tr><td><u>Mean WASO, min (SD),</u>
Baseline
Week 1
1 month
6 months</td><td>
70.7 (72.8)
69.0 (120.8)
62.8 (77.2)
48.2 (59.4)</td><td>
83.2 (120.7)
48.2 (102.4)
47.4 (77.7)
44.2 (74.2)</td><td>
.3038
<.0001
<.0001
.0032</td></tr>
<tr><td><u>Mean Awakenings/night, no</u>
Baseline
Week 1
1 month
6 months</td><td>
3.5 (2.8)
2.8 (2.1)
2.8 (2.6)
2.6 (2.7)</td><td>
3.2 (2.3)
2.2 (1.7)
2.1 (1.4)
1.9 (1.5)</td><td>
.2098
.0013
<.0001
<.0001</td></tr>
<tr><td><u>Mean Nights Awakened/wk, no</u>
Baseline
Week 1
1 month
6 months</td><td>
5.6 (1.8)
5.2 (2.2)
5.0 (1.9)
4.7 (2.4)</td><td>
5.3 (2.0)
4.3 (2.4)
4.1 (2.2)
3.9 (2.5)</td><td>
.1172
.0001
<.0001
.0001</td></tr>
<tr><td>Sleep Duration</td><td></td><td></td><td></td></tr>
<tr><td><u>Mean Total Sleep Time, min</u>
Baseline
Week 1
1 month
6 months</td><td>
303.6 (78.3)
322.3 (73.8)
333.1 (69.8)
339.3 (77.1)</td><td>
302.4(123.2)
372.5 (85.7)
373.9 (67.5)
378.3 (72.3)</td><td>
.1986
<.0001
<.0001
<.0001</td></tr>
<tr><td>Sleep Quality</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>1194 screened/791* eligible/788 randomized/471 (59.5%) completed
* 3 patients (1 placebo and 2 eszopiclone discontinued study prior to receiving study med)
<u># Pts. Voluntary withdrawal (%)</u>
eszopiclone 3 mg: 82 (13.8)
placebo: 51 (26)
<u># Pts. Protocol violations (%)</u>
eszopiclone 3 mg: 17 (2.9)
placebo: 7 (3.6)
<u>#Pts Adverse Events: (%)</u>
eszopiclone 3mg : 76 (12.8)
placebo: 14 (7.1)
<u>Lost to follow-up (%)</u>
eszopiclone: 52 (8.7)
placebo: 8 (4.1)
<u>Other reasons for discontinuing-(not reported) (%)</u>
eszopiclone 3mg: 8 (1.3)
placebo: 5 (2.6)

Table 2: Treatment-Related Adverse Events*
<table>
<tr><th>Adverse Events</th><th>Placebo n=195 n (%)</th><th>ESZ** 3mg n=593 n (%)</th></tr>
<tr><td>Abdominal pain</td><td>11 (5.6)</td><td>48 (8.1)</td></tr>
<tr><td>Accidental injury</td><td>11 (5.6)</td><td>43 (7.3)</td></tr>
<tr><td>Asthenia</td><td>11 (5.6)</td><td>26 (4.4)</td></tr>
<tr><td>Back pain</td><td>6 (3.1)</td><td>45 (7.6)</td></tr>
<tr><td>Diarrhea</td><td>14 (7.2)</td><td>45 (7.6)</td></tr>
<tr><td>Dizziness</td><td>6 (3.1)</td><td>58 (9.8)</td></tr>
<tr><td>Dry Mouth</td><td>3 (1.5)</td><td>39 (6.6)</td></tr>
<tr><td>Dyspepsia</td><td>13 (6.7)</td><td>41 (6.9)</td></tr>
<tr><td>Headache</td><td>37 (19)</td><td>116 (19.6)</td></tr>
<tr><td>Infection</td><td>13 (6.7)</td><td>94 (15.9)</td></tr>
<tr><td>Nausea</td><td>11 (5.6)</td><td>67 (11.3)</td></tr>
<tr><td>Pain</td><td>12 (6.2)</td><td>67 (11.3)</td></tr>
<tr><td>Pharyngitis</td><td>10 (5.1)</td><td>59 (9.9)</td></tr>
<tr><td>Rash</td><td>6 (3.1)</td><td>31 (5.2)</td></tr>
<tr><td>Rhinitis</td><td>9 (4.6)</td><td>42 (7.1)</td></tr>
<tr><td>Sinusitis</td><td>11 (5.6)</td><td>25 (4.2)</td></tr>
<tr><td>Somnolence</td><td>5 (2.6)</td><td>54 (9.1)</td></tr>
<tr><td>Unpleasant taste</td><td>11 (5.6)</td><td>155 (26.1)</td></tr>
</table>
*Adverse Events reported occurring at a rate ≥ 5% in any group; **eszopiclone
</td>
</tr>
</table>

			Mean Sleep Quality			
			Baseline	3.5 (2.0)	3.5 (2.0)	.5782
			Week 1	4.4 (2.2)	6.0 (2.2)	<.0001
			1 month	5.0 (1.7)	6.2 (1.8)	<.0001
			6 months	5.5 (1.8)	6.4 (1.8)	<.0001
			Next day function			
			Mean Daytime Ability to Function			
			Baseline	5.6 (1.8)	5.6 (2.1)	.9032
			Week 1	5.6 (2.0)	6.8 (1.9)	<.0001
			1 month	6.1 (1.7)	6.8 (1.6)	<.0001
			6 months	6.2 (1.8)	6.8 (1.7)	<.0001
			Mean Daytime Alertness			
			Baseline	4.7 (2.0)	5.6 (2.1)	.5659
			Week 1	4.9 (2.2)	6.1 (2.1)	<.0001
			1 month	5.5 (1.6)	6.3 (1.7)	<.0001
			6 months	5.9 (1.7)	6.5 (1.7)	<.0001
			Mean Sense of Physical Well-being			
			Baseline	5.9 (2.0)	5.9 (2.1)	.8387
			Week 1	5.7 (2.1)	6.6 (2.0)	<.0001
			1 month	6.1 (1.7)	6.6 (1.6)	<.0001
			6 months	6.1 (1.8)	6.7 (1.7)	.0002

* using last Observation Carried Forward technique; **eszopiclone

Adverse Events

- Overall, all-causality adverse event rates were 81.1% for the eszopiclone group, compared with 70.8% for the placebo group

Severity of Adverse Events

- Mild or moderate in severity (placebo 89.2%; eszopiclone, 87.7%). Most common adverse events were unpleasant taste, headache, infection, pain, nausea, and pharyngitis.

Adverse Events Related to Treatment

- "Unknown" (placebo 6.2%; eszopiclone 6.4%)
- "Possibly related" (placebo 25.1%; eszopiclone 29.5%)
- "Probably or definitely" (placebo 7.2%; eszopiclone 22.6%)

The percentage of new events after treatment discontinuation occurred in 10.7% in the placebo compared to 11.2% in the placebo. No reports of seizures, hallucinations, or perceptual-disturbance events. One report of anxiety in the eszopiclone group.

Study Conclusions

- **Short-term efficacy (data from week 1):**
  - **Sleep Induction**: The median sleep latency per night was 30 minutes for the eszopiclone group (decrease of 30 minutes from baseline) and 60 minutes for placebo, (decrease of 15 minutes from baseline) p<.0001.
  - **Sleep maintenance:** The median WASO for patients taking eszopiclone 3mg was 20 minutes (60 at baseline) compared with 45 minutes for the placebo group (no change from baseline) (p<.0001). The median number of awakenings per night was similar in both groups. The median number of nights awakened per week was less with eszopiclone 3mg compared with placebo, 4 vs. 6.5, respectively. The median total sleep time increased by 75 minutes with eszopiclone compared to an increase of 30 minutes in the placebo group. A 50% increase in sleep quality (4 at baseline to 6) was seen in patients taking eszopiclone while the score for patients receiving placebo did not change. The median score for daytime ability to function was 5 at baseline and increased to 7 in the eszopiclone group compared to no change in the placebo group. The median score for daytime alertness increased from 5 at baseline to 6 in the eszopiclone group compared to no change in the placebo group. The median score for sense of physical well-being was 6 at baseline and increased to 7 with eszopiclone compared to no change in patients in the placebo group.
- **Long-term efficacy (6 months):**
  - **Sleep Induction:** The median sleep latency per night was 30 minutes for the eszopiclone group and 45 minutes for placebo (p<.0001).
  - **Sleep Maintenance**: The median WASO was 21 minutes vs. 30 minutes for eszopiclone and placebo, respectively; p = .0032. The median number of awakenings per night was 2 for patients taking placebo and 1.6 for eszopiclone (p <.0001), while the median number of nights awakened per week was 5.2 for placebo compared with 4 for eszopiclone (p=.0001). The median total sleep time was 382 minutes for the eszopiclone group and 345 minutes for the placebo group,(p<.0001). The total sleep time was 82.5 minutes longer with eszopiclone 3mg at 6 months compared to baseline. The median sleep quality scores increased from 4 at baseline to 6.5 with eszopiclone compared to the increase from 4 to 5.5 in patients taking placebo, p <.0001. The median score for daytime ability to function was 5 at baseline and increased to 7 in the eszopiclone group compared to the increase of 0.3 seen in the placebo group (6 at baseline to 6.3). The median score for daytime alertness increased from 5 at baseline to 6.8 in the eszopiclone group compared to 5 at baseline in the placebo group to 6 at 6 months. The median score for the sense of physical well-being was 6 at baseline and increased to 6.9 with eszopiclone compared to the increase from 6 at baseline to 6.3 in the placebo group.
- **Safety:**
  - Overall, high discontinuation rates existed (not statistically different) in the eszopiclone and placebo group (39.5% and 43.4%, respectively). The rate of discontinuation due to adverse events was 7.1% in the placebo group and 12.8% in the eszopiclone group (p < .05), while the rate of voluntary withdrawals was 26% in the placebo group compared with 13.8% for the eszopiclone group (p<.001). The most common reasons for discontinuation were were somnolence (2.2% vs. 1.5%), depression (2.0% vs. 0%), unpleasant taste (1.7% vs. 0.5%), headache (0% vs. 2.0%), asthenia (1.0% vs. 1.5%), and insomnia (0% vs. 1.5%) for eszopiclone compared to placebo, respectively.

- The adverse event accounting for the majority of the "probably" or "definitely related" to the study drugs was unpleasant taste, which led to a discontinuation in 0.5% of patients taking placebo and 1.7% patients taking eszopiclone.

Quality Assessment (Good)- Long term study- (6 months)- although perhaps not generalizeable to VA population.

Of note, 471 patients continued in the 6 months, open-label extension. Data available in abstract. Long term treatment was well tolerated and was not associated with development of tolerance or significant adverse events upon discontinuation.

- Mean age of 44 years –primarily Caucasian females, 13% African Americans
- Multiple Exclusions (see above)
- Co-morbidities not reported
- Only the 3mg dose of eszopiclone was utilized
- Study done in patients with primary insomnia per DSM-4 criteria. DSM-4 criteria indicates for at least a month the person main complaint has been trouble going to sleep, staying asleep or feeling unrested. The insomnia, or resulting daytime fatigue, causes clinically important distress or impairs work, social or personal functioning

Three of the authors (including the primary author) are consultants, investigators and advisory board members to Sepracor. One author is a consultant to Sepracor. Three of the authors are Sepracor employees.

6-week Polysomnographic Study in Adults with Primary, Chronic Insomnia

<table>
<tr><th>Trial/ Purpose</th><th>Inclusion/Exclusion/Endpoints</th><th>Treatment</th><th>Results</th><th>Adverse Events/Withdrawals</th></tr>
<tr>
<td>Zammit et al.[11] 2004

R, DB, PC, P, MC

(40 different sites in the United States and one site from Canada acknowledged)

Purpose:

1. To evaluate the efficacy and safety of eszopiclone 3mg vs. placebo

2. To evaluate the efficacy and safety of eszopiclone 2mg

3. To evaluate tolerance, rebound and withdrawal

4. To assess the next-day residual effects throughout 6</td>
<td>Inclusion criteria:
Adults 21-64 years of age who met DSM-IV criteria for chronic primary insomnia and reported ≤ 6.5 h of sleep/night and required > 30 min. to fall asleep each night for at least 1 month were eligible to be screened.

Screening: 2 consecutive nights in sleep lab for PSG recording to rule out other sleep disorders. Single-blind placebo was administered 30 min. before lights were turned off. PSG eligibility criteria included:

1. LPS- Latency to Persistent Sleep mean of ≥ 20 min. (neither night less than 15 min)

2a. TST- Total Sleep Time mean of ≤ 420min
OR
2b. WASO- Wake time After Sleep Onset mean of at least 20 min. (neither night less than 15 min.)

Exclusion criteria:
• Any unstable medical abnormality or acute illness</td>
<td><u>6 wks duration</u>

Eszopiclone 2mg or 3mg at bedtime vs. placebo x 44 consecutive nights, followed by 2 nights of single-blind placebo to assess the occurrence of rebound insomnia. Safety visit was completed within 5-7 days after the final dose of study medication.

Efficacy-assessment:

At sleep lab:

• Concomitant meds reviewed, medical history updated, and AE assessed
• Profile of Mood States questionnaire -(POMS)
• Evening questionnaire- assessing daytime alertness and the ability to think clearly and function with an 11 point Likert scale. Patients were required to call an automated interactive voice response system (IVRS).
• Polysomnography (PSG)</td>
<td>Baseline: Mean age 39.8 years (range, 21-64); 64.6% female; 66.2% Caucasian. A significantly higher mean body mass index (BMI kg/m^3) relative to placebo was seen in the eszopiclone 2mg and 3mg groups compared to placebo (28 vs. 27.1* vs. 26.1 respectively; *p<.05 compared to placebo)

Table 1. Polysomnography (PSG) Sleep Efficacy Results
<table>
<tr><th>Endpoints</th><th>Placebo (n=99)</th><th>ESZ* 2mg (n=104)</th><th>ESZ* 3mg (n=105)</th></tr>
<tr><td>Primary
<u>Mean LPS¶ in min (SD)</u></td><td></td><td></td><td></td></tr>
<tr><td>Baseline</td><td>38.4 (35.1)</td><td>39.5 (36.1)</td><td>42.8 (41.6)</td></tr>
<tr><td>DB Average**
p value†</td><td>33.0 (22.6)</td><td>23.0 (24.9)
≤ 0.001</td><td>18.0 (15.7)
≤ 0.001</td></tr>
<tr><td>Secondary
<u>Mean % sleep efficiency^ (SD)</u></td><td></td><td></td><td></td></tr>
<tr><td>Baseline</td><td>81.3 (10.9)</td><td>81.2 (12.6)</td><td>81.3 (13.0)</td></tr>
<tr><td>DB Average**
p value†</td><td>83.5 (8.9)</td><td>86.5 (7.6)
<0.01</td><td>88.8 (5.7)
≤ 0.001</td></tr>
<tr><td><u>Mean WASO§ in min (SD)</u></td><td></td><td></td><td></td></tr>
<tr><td>Baseline</td><td>56.5 (41.7)</td><td>55.7 (51.3)</td><td>51.3 (44.7)</td></tr>
<tr><td>DB Average**
p value†</td><td>50.0 (34.5)</td><td>44.5 (29.4)</td><td>38.0 (26.7)
<0.01</td></tr>
</table>
* eszopiclone;¶ LPS= Latency to Persistent Sleep defined as the time from lights out to the first 10 consecutive minutes of sleep, averaged over the double-blind period (mean of Nights 1, 15 and 29) for PSG data; mean of Nights 1, 15, 29, and 43/44 for the self-report data; *DB Average= Double Blind Average of Nights 1, 15 and 29 of the PSG data and Nights 1, 15, 29, 43/44 for the self-reported sleep data; † vs. placebo; ^ sleep efficiency= ratio of total sleep time to the total time in bed of 8h x 100; § WASO= number of wake epochs (30-s intervals] after the onset of</td>
<td>669 pts screened/ 308 eligible/308 enrolled/292 pts completed study (94.8%)

<u># Pts. Voluntary withdrawal</u>
Eszopiclone 3 mg: 2
Eszopiclone 2mg: 2
Placebo: 2

<u># Pts. Protocol violations</u>
Eszopiclone 2 mg: 2
Placebo: 2

<u>#Pts Adverse Events:</u>
Eszopiclone 2mg : 3 (1= headache; 1=headache, N, V; 1=flu)

<u>Other reasons for discontinuing-(not reported)</u>
Eszopiclone 3mg: 2
Placebo: 1</td>
</tr>
</table>

weeks of nightly treatment in patients with chronic primary insomnia

- Any pertinent drug sensitivities, abnormalities in drug metabolism
- Periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, or sleep apnea
- Pregnancy or lactating females
- Patients with Axis I or Axis II psychiatric disorders, hx of substance abuse or dependence, drinks ≥ 2 alcoholic beverages/day
- Any drugs known to affect sleep (psychotropic, hypnotics, antihistamines) within 3 days, any herbal supplements or melatonin within 14 days, St. John's Wort within 30 days or any drug affecting hepatic or renal clearance capacity within 30 days before screening was not permitted

Primary Endpoints:
1. Polysomnography (PSG) determined latency persistent sleep (LPS), defined as the time from lights out to the first 20 consecutive epochs of sleep, averaged over the double-blind period (mean of Nights 1, 15, and 29 for PSG data; mean of Nights 1, 15, 29, and 43/44 for self-report data) between 3mg eszopiclone and placebo.

Secondary: Endpoints:
1. Mean PSG sleep efficiency (ratio of total sleep time to the total time in bed of 8 hr x 100) expressed as a percentage
2. WASO: (defined as the number of wake epochs (30 second intervals) after the onset of persistent sleep until the end of recording, divided by 2)

on Nights 1, 15, 29

After 8 hours of PSG recording:

- Morning questionnaire: (nights 1, 15, 29) and at home on the morning after nights 43/44) Patients reported sleep latency, total sleep time, number of awakenings, WASO, quality of sleep, depth of sleep and morning sleepiness from the previous night.
- Digit-Symbol Substitution Test (DSST)- evaluate next day residual effects on nights 1, 15, and 29 conducted 1h-1.5 h after awakening.

At home:

- Call IVRS each evening prior to study medication to report estimates of daytime alertness and ability to function.

Safety-assessment:

Physical and laboratory measures including clinical lab tests, ECGs, vital signs, physical and neurological examinations and the occurrence of adverse events.

persistent sleep until the end of recording, divided by 2.

Table 2: Summary of Patient-Reported Efficacy Data

Subjective Measure	PBO* (n=99)	ESZ** 2mg (n=10)	ESZ** 3mg (n=105)
Mean LPS in min (SD)	58.4 (42.9)	48.0 (69.6)	44.5 (68.8)
p value†		<0.0001	< 0.001
Mean total sleep time in min (SD)	363.8 (63.5)	381.8 (63.9)	411.8(124)
p value†		.02	<0.0001
Mean number of awakenings (SD)	3.2 (1.9)	2.9 (1.7)	3.0 (2.2)
p value†		.2956	.17
Mean WASO in min (SD)	49.1 (36.1)	53.4 (48.1)	41.2 (39.0)
p value†		.68	.02
Mean mm quality of sleep (SD) §	49.0 (18.1)	54.4 (18.7)	54.4 (18.7)
p value†		.04	.007
Mean mm depth of sleep (SD) ¶	50.5 (17.8)	57.8 (19.0)	55.7 (15.7)
p value†		.005	.0457

*PBO: placebo; **ESZ: eszopiclone

Table 3: Treatment-Related Adverse Events*

Adverse Event*	Placebo n= 99 n (%)	ESZ** 2mg n=104 n (%)	ESZ** 3mg n=105 n (%)
Abnormal Dreams	2 (2)	3 (2.9)	2 (1.9)
Nervousness	2 (2.0)	5 (4.8)	0
Back pain	2 (2.0)	1 (1.0)	4 (3.8)
Dizziness	4 (4.0)	3 (2.9)	5 (4.8)
Dry mouth	2 (2.0)	5 (4.8)	6 (5.7)
Headache	8 (8.1)	13 (12.5)	12 (11.4)
Somnolence	3 (3.0)	8 (7.7)	8 (7.6)
Unpleasant Taste	3 (3.0)	17 (16.3)	35 (33.3)

*Adverse events presented are any that occurred during the double-blind treatment period considered by the investigator to be definitely, probably, possibly, or of unknown relationship to treatment, occurring at a rate ≥ 2% and greater in either eszopiclone group than placebo; **Eszopiclone

Table 4: New CNS and potentially CNS-related events after treatment discontinuation

Adverse Event	Placebo n= 99 n (%)	ESZ* 2mg n=104 n (%)	ESZ* 3mg n=105 n (%)
Any	18 (18.2)	12 (11.5)	16 (15.2)
Accidental Injury	4 (4.0)	1 (1.0)	2 (1.9)
Abnormal Dreams	0	0	2 (1.9)
Anxiety	0	2 (1.9)	1 (1.0)
Back Pain	2 (2.0)	1 (1.0)	0
Dizziness	2 (2.0)	0	0
Hyper-aesthesia	0	0	1 (1.0)
Headache	2 (2.0)	0	1 (1.0)
Nausea	2 (2.0)	2 (1.9)	0
Neurosis	0	0	1 (1.0)
Pain	1 (1.0)	1 (1.0)	0
Photo-sensitivity	1 (1.0)	1 (1.0)	0

*Eszopiclone

Study Conclusions

- Eszopiclone did not adversely affect mood, as measured by POMS (reported in study but data not shown). Treatment was well tolerated.
- Sleep Stages 3 and 4 were not significantly different between the active drug groups and placebo. There was a small but statistically significant increase in Stage 2 (219min, 244min, and 252 min, for placebo, 2mg, and 3mg group, respectively; p<0.05 for each active med vs. placebo). There were no statistically significant differences in the total time in REM between the placebo and eszopiclone groups.
- No tolerance to treatment with the 3mg dose was demonstrated as performed on PSG findings for LPS, sleep efficiency and WASO on Nights 1, 15, and 29.
- Rebound Insomnia: None in the 3mg group relative to study baseline in objective LPS, sleep efficiency, or WASO on the individual nights or the average of the two nights following withdrawal of the study drug. Of note, the 3mg group appeared to maintain efficacy post discontinuation of dosing with an 8.5 min decrease in LPS and a 3.7% increase in sleep efficiency on night 46, p<0.05.
- Next-day residual effects measured by DSST scores were not significantly different for either treatment group relative to placebo at any time point.
- Report of daytime alertness and ability to function as assessed by the Evening Questionnaire improved in patients who received eszopiclone 3mg compared with those who received placebo. These differences were statistically significant at week 2; p<0.05.
- Withdrawal effects: (single-blind placebo run-out phase) eszopiclone 2mg; 11.5%, eszopiclone 3mg; 15.2%, vs. placebo; 18.2% (see Table 4)
- Sleep maintenance (WASO) as measured by PSG was 25% lower for the 3mg group vs. placebo; p< 0.05.
- 28.9 minute less to achieve the primary endpoint was observed with eszopiclone 3mg vs. placebo.

Quality Assessment (Good)-although perhaps not generalizeable to VA population

- Mean age of 40 years –primarily Caucasian females. Patients between the ages of 60-64: 5.1% (n= 5) in placebo, 4.8% (n= 5) in eszopiclone 2mg , 2.9% (n= 3) in the eszopiclone 3mg group
- Multiple Exclusions (see above); Co-morbidities were not reported
- Study done in patients with primary insomnia per DSM-4 criteria. DSM-4 criteria indicates for at least a month the main complaint has been trouble going to sleep, staying asleep or feeling unrested. The criteria also states that the insomnia, or resulting daytime fatigue, causes clinically important distress or impairs work, social or personal functioning.

Study supported by Sepracor

Treatment of Transient Insomnia in an Adult Population

Trial/ Purpose	Inclusion/Exclusion/Endpoints	Treatment	Results	Adverse Events/Withdrawals
Rosenberg et al.[12] 2004 R, DB, PC, MC (15 study centers in US) Purpose:	**Inclusion Criteria:** Patients between 25 and 5**0** years of age with a body mass index (BMI) of at least 16 but no more than 30 kg/m^2. No history of insomnia Normal nightly sleep pattern including a standard bedtime (between 2100 and 2400), normal sleep onset (<30 min), normal sleep duration (between 6.5 and 10 h), and no report of daytime	**<u>1 single nighttime dose</u>** Eszopiclone 1, 2, 3, 3.5 mg or placebo 30 minutes before bed in a 1:2:2:2:2 ratio. **Safety-assessment:**	**Baseline:** Mean age 33 years; 43.7% males; 56.3% female; 78% Caucasian, 16.8% African-American. No statistically significant between-group differences in weight or BMI. **Polysomnography (PSG) Efficacy Results:** • **Median Latency to Persistent Sleep (LPS): (minutes)** all doses except 1mg; p≤0.0001 **Median Wake Time After Sleep Onset (WASO): (minutes)** all doses; p<0.05 • **Median Number of Awakenings**: p<0.005 for eszopiclone 3 and 3.5mg vs. placebo	436 randomized/436 Completed study (100%) Table 2: Percent of adverse events, regardless of relationship to treatment Placebo (n= 98) / ESZ 1mg (n=47) / ESZ 2mg (n=97) / ESZ 3mg (n=98) / ESZ 3.5mg (n=96) Any Event: 18.4 / 23.4 / 30.9 / 33.7 / 28.1 Abdominal pain: - / - / - / - / 2.1

Dose-finding study

Evaluate the safety and efficacy of eszopiclone in healthy patients using a "first-night effect" model of transient insomnia.

functioning problems due to sleep.

Subjects agreed not to consume any caffeinated or alcoholic beverages after 1400 hours on the day of the study

Exclusion Criteria:

- previously slept in a sleep laboratory
- symptoms of a primary sleep disorder
- known hypersensitivity to zopiclone, other hypnotics or any substance in the study formulation
- unstable medical abnormality or chronic disease
- history of a psychiatric disorder or clinically significant lab abnormality of the cardiovascular, respiratory, hepatic, or renal systems
- consumed OTC analgesics within 7 days of the study
- used tobacco or nicotine products or smoking cessation within 3 months
- daily caffeine greater than 180mg

Endpoints:

Primary Objective (assessed by PSG) Endpoints:

1. Latency to Persistent sleep (LPS) (time from lights out to the beginning of 10 uninterrupted minutes of sleep)

Objective Secondary Efficacy Endpoints

1. WASO-total amount of time spent awake after the onset of persistent sleep)
2. Sleep efficiency
3. # of awakenings
4. Sleep architecture (median percentage of time spent in NREM Stages 1,2,3,4 and REM)

Self-reported secondary efficacy endpoints: (using morning questionnaire)

1. Sleep latency, total sleep time
2. number of awakenings
3. WASO
4. quality of sleep (4 points scale)
5. depth of sleep (4 points scale)

Clinical laboratory tests, 12-lead electrocardiograms, vital signs, physical and neurologic examinations, and occurrence of adverse effects. Digital Symbol Substitution Test (DSST) was used to determine residual next-day psychomotor drug effects following 8 hours of PSG monitoring.

- **Sleep efficiency:(%)**
  p<0.02 all doses vs. placebo

Subjective Efficacy Measures: (Table 1)

- **Median Latency to persistent sleep (LPS)**: The LPS in patients treated with eszopiclone 1mg was not significantly different than placebo. Patients treated with eszopiclone 2, 3, and 3.5mg had significantly shorter LPS compared to placebo; ($p \leq 0.001$).
- **Median Wake Time After Sleep Onset (WASO)**-All patients taking eszopiclone had significantly less WASO compared to placebo; ($p \leq 0.05$).
- **Median Number of Awakenings:** Subjects treated with eszopiclone 1mg and 2mg had fewer awakenings than placebo but it was not statistically different. Subjects taking 3mg and 3.5mg had significantly fewer awakenings compared to placebo; ($p<0.005$).
- **Median Sleep Efficiency:** All subjects regardless of the dose of eszopiclone had significantly higher sleep efficiency than placebo; ($p \leq 0.02$)

Table 1: Summary of Subjective Efficacy measures (morning Questionnaire)

	PBO (n=98)	ESZ 1mg (n=47)	ESZ 2mg (n=97)	ESZ 3mg (n=98)	ESZ 3.5mg (n= 96)
Median LPS (min)	15	10*	10***	10***	8***
Median Total sleep time (min)	460	460	470**	474.5**	478***
Median number of awakenings	2	2*	2*	1***	1***
Median WASO (min)	10	10	5	5**	3**
Median morning sleepiness (mm[a])	67	77	74	79*	78*
Sleep quality[b] % reporting good-excellent	52	65.9	78.4***	78.5***	85.4***
% reporting poor-fair	46.9	34	21.6***	20.4***	13.5***
Sleep depth [c] % reporting deep-very deep	55.1	76.6**	79.4**	81.7***	82.3***
% reporting very light-light	43.9	23.4**	20.6**	17.3***	16.6***

PBO: Placebo; ESZ= eszopiclone;*$p \leq 0.05$, **$p \leq 0.01$; ***$p \leq 0.0001$

Face edema	-	-	-	1.0	-
Headache	2.0	2.1	2.1	4.1	1.0
Abnormal dreams	1.0	-	-	2.1	1.0
Anxiety	1.0	-	-	-	-
Dizziness	-	-	1.0	-	4.2
Halluci-nations	-	-	-	1.0	-
Nervousness	1.0	-	-	2.0	-
Nystagmus	-	-	-	1.0	1.0
Somnolence	4.1	4.3	6.2	5.1	4.2
Rash	-	2.1	-	1.0	1.0
Unpleasant taste	7.1	17.0	21.6	21.4	19.8

ESZ=eszopiclone

			[a] Measured by a visual analog scale, where 0 mm= very sleepy and 100mm = not at all sleepy [b] Four point categorical scale from poor to excellent; (percentages do not add up to 100 due to one missing data point) [c] Four point categorical scale from very light to very deep; (percentages do not add up to 100 due to one missing data point)	

Study Conclusion (after one-dose)

- All doses were more effective than placebo in inducing and maintaining sleep in this model of transient insomnia following a single dose in healthy, normal sleeping participants.
- Compared with placebo, subjects treated with eszopiclone 2, 3, and 3.5mg had significantly decreased time to sleep onset, WASO, and increased sleep efficiency evaluated via PSG. Subjects treated with eszopiclone 3 and 3.5mg had significant decreases in number of nighttime awakenings evaluated via PSG compared with placebo; (p<.005).
- Subjects treated with the eszopiclone 1mg had significantly decreased WASO compared to placebo; (p<0.05). Increased sleep efficiency was also observed with eszopiclone 1mg compared to placebo; (p<.02) (evaluated via PSG)
- On subjective efficacy measures, all doses of eszopiclone significantly improved sleep latency and decreased the number of awakenings. Eszopiclone 2, 3 and 3.5mg significantly increased the median total sleep time by 10min, 14.5min, and 18 min, respectively compared to baseline.
- All doses of eszopiclone improved sleep quality.
- Safety and tolerability between placebo and eszopiclone (all doses) were similar. Unpleasant taste was the most frequent dose-related adverse event reported more often in eszopiclone than placebo.

Quality Assessment (Good)- Dose Finding study- (one-single dose in transient insomnia) although not generalizeable to VA population

- Healthy, normal sleeping patients; mean age of 33 years –primarily Caucasian females, 16.8% African Americans
- Multiple Exclusions (see above)

One of the authors was an employee of Sepracor. Study was supported by Sepracor.

2 week Efficacy and Safety Study in Elderly Patients with Primary Insomnia

Trial/ Purpose	Inclusion/Exclusion/Endpoints	Treatment	Results	Adverse Events/Withdrawals
Scharf et al.[17] 2005 R, DB, PC, MC, outpatient setting Purpose: Evaluate the patient-reported efficacy and safety of eszopiclone administered nightly for 2 weeks in community-dwelling	**Inclusion Criteria:** Patients between 65 and 85 years of age who met the DSM IV criteria for primary insomnia confirmed via a 60-90 minutes medical history interview. Patients with comorbid conditions that were not suspected to affect sleep were permitted unless the clinical pattern was potentially unstable (e.g., previous clinically significant CV difficulty, malignant carcinoma, severe COPD) Substances affecting sleep (psychotropics, hypnotics, herbal supplements, antihistamines) were discontinued prior to screening (4-18 days prior to randomization) and prohibited during the study. Alcohol use was limited to ≤2 drinks per day and not consumed	**2 wks duration** Eszopiclone 1, 2, or placebo x 14 consecutive days **Safety-assessment:** Clinical laboratory tests, 12-lead electrocardiograms, vital signs, physical and neurologic examinations, and occurrence of adverse effects.	**Baseline:** Mean age 72 years; (range 64-85); 42.5% males; 57.5% female; 96.5% Caucasian, 2.2% African-American, 1.3% Hispanic. No statistically significant between-group differences in body mass index (BMI); range 18-43). The top 5 comorbid conditions were HTN, hypercholesterolemia, hypothyroidism, osteoarthritis and presbyopia. The top 5 concomitant medications included: ASA, estrogen, calcium, levothryoxine and APAP. **Subjective Efficacy Measures: (Table 1)** Four data points for sleep latency and 1 measure of WASO were considered to be erroneous and were not included in the efficacy analysis for sleep latency and WASO. The outliers for sleep latency were: placebo, 11 hours; placebo, 22 hrs; eszopiclone 2mg, 11.2 hrs; and eszopiclone 1mg, 20.3 hrs. The outlier for WASO was with eszopiclone 2mg, 20.3 hours. The erroneous data points for WASO and sleep latency were pre-identified and predefined in the protocol if the measurements were greater or equal to 540 minutes (≥ 9 hours). [Personal communication with Sepracor -8/3/05]	353 screened/231 (65%) randomized/210 (90.9%) completed study Incidence of Adverse Events: Placebo 40% (29/80); eszopiclone 1mg 40% (29/72); eszopiclone 2mg (34/79) 43%. Number of patients discontinued due to AE Placebo, 6.3% (n=13); eszopiclone 1mg, 1.4% (n=3); eszopiclone 2mg, 2.5% (n=5) Table 3: Incidence (%) of the Most Common (≥5%) Treatment-Related Adverse events Placebo n=80* / ESZ 1mg n=72* / ESZ 2mg n=79* Headache: 15.0 / 15.3 / 15.2

elderly patients with primary insomnia.	within 2 hours of taking study medication. **Exclusion Criteria:** ● Presence of any significant neurologic, medical, laboratory, electrocardiographic, or psychiatric conditions that could have been the primary cause of the sleep complaint or that were significantly affecting sleep (e.g., pain or substance abuse) ● Prior history of severe COPD, history of any condition that could interfere with the absorption of orally administered medicine or prior participation in an investigational study less than 30 days prior to screening were excluded. **Endpoints:** **Primary Endpoints:** • Sleep latency (assessed by IVRS-morning questionnaire and averaged over the double-blind period). Primary analysis was the comparison between 2mg eszopiclone and placebo. • Total Sleep Time (TST)-assessed by IVS-morning questionnaire and averaged over the double-blind period) **Secondary variables evaluated via morning questionnaire included:** 1. WASO -total amount of time spent awake after the onset of persistent sleep 2. # of awakenings 3. morning sleepiness 4. quality of sleep 5. depth of sleep **Other daytime function variables Secondary Endpoints: (assessed by IVRS-evening questionnaire)** 1. rating of day-time alertness 2. ability to function 3. sense of physical well-being 4. # of naps taken 5. length of naps Function was assessed with an 11-point Likert scale (0-10, with 0 representing the least desirable outcome (e.g. very		In addition, a hierarchical testing strategy was utilized to control for multiple comparison. For the primary endpoint, the eszopiclone 2mg group was first compared with placebo and if significant at the 2-sided 5% significance level, the test of TST double-blind average 2 mg vs. placebo was considered to be statistically significant if the p value was .05 or less. If the test for sleep latency, 2mg vs. placebo was not statistically significant, the test for TST would not have been considered statistically significant regardless of the p value. The same prospective hierarchical approach was used for the comparison between 1mg and placebo, although an additional requirement for statistical significance was that the comparison between 2 mg and placebo for the same endpoint was also significant. No multiple comparison adjustments were applied for the secondary analyses. Table 1: Summary of Double-Blind Average-Efficacy Measures (Morning Questionnaire)* **PBO (n=80) / ESZ 1mg (n=72) / ESZ 2mg¶ (n=79)** Median Sleep latency, (min): 52 / 35.9** / 36.2 p =.0034 Median Total Sleep Time (min): 345 / 352.1 / 383.2 p=.0003 Median WASO (min): 58.1 / 63.5 / 49.5 p =.0423 Median number of awakenings: 1.9 / 2.0 / 1.6 Sleep quality[a]: 6.1 / 6.5 / 7.4 p=.0025 Sleep depth [b]: 6.2 / 6.4 / 7.2 p=.0015 Double-Blind Average-Daytime Function Results* Median Daytime Alertness[c]: 6.9 / 7.0 / 7.8 p=.0223 Median Physical Well-Being[a]: 7.2 / 7.6 / 8.0 p=.0474 Median Morning sleepiness[d]: 6.9 / 6.8 / 7.5 p=.0547 Median Daily Ability to Function[a]: 7.3 / 7.5 / 8.0 p=.0579 PBO: Placebo; ESZ= eszopiclone;**p < 0.05 vs. placebo; ¶ statistical tests are based on the mean ranks between 2mg vs. placebo *Double-blind average medians were determined from the data obtained during the double-blind period and were not the average of the medians for the first and second weeks. [a] 11-point Likert scale from 0=poor to 10-excellent [b] 11-point Likert scale from 0=very light to 10=very deep [c] 11 point Likert scale from 0=drowsy to 10=alert. [d] 11 point Likert scale from 0=very sleepy to 10 = not at all sleepy Table 2: Summary of Double-Blind Average Change from Baseline-Subjective Efficacy measures *	Dyspepsia: 2.5 / 5.6 / 1.3 Somnolence: 8.8 / 6.9 / 3.8 Rash: - / 2.1 / - Unpleasant taste: 1.3 / 8.3 / 11.4 ESZ=eszopiclone;* total number for each treatment group was confirmed via personal communication with Sepracor-8/3/05.

	sleepy, poor sleep quality) and 10 representing the best outcome (e.g. not sleepy at all, excellent sleep quality) Quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). It measures 16 separate QOL dimensions, (physical health, mood, social and family relationships, ability to function in daily life, perception of ability to do work or hobbies, overall sense of well-being, and overall life satisfaction and also includes a global summary). Participants rated each item as very poor, poor, fair, good, or very good based on their perception of the previous week.		See table below Eszopiclone 2mg significantly decreased patient-reported sleep latency (p=.0059), WASO (p=.0009), number of awakenings (p=.0170) and sleep depth (p=.0064) compared with placebo over the double-blind period. No significant differences were observed over the double-blind period between eszopiclone 1mg and placebo group. Patient reported daytime alertness and sense of physical well-being were significantly higher (p≤.05) in the eszopiclone 2mg group compared with placebo.	

	PBO (n=80)	ESZ 1mg (n=72)	ESZ 2mg¶ (n=79)
Median Sleep latency, (min)	-5.3	-10.9	-10.3 p =.0059
Median Total Sleep Time (min)	14.3	51.7	75.1 p=.0002
Median WASO (min)	5.7	-24.0	-30.6 p=.0009
Median number of awakenings	-0.1	-0.5	-0.6 p=.0170
Sleep quality[a]	0.9	1.4	1.7 p=.0018
Sleep depth[b]	1.1	1.6	2.1 p=.0064

*Double-blind Change, change from baseline to the end of the double-blind period. ¶ statistical tests are based on the mean ranks between 2mg vs. placebo, WASO=Wake time after sleep onset
[a] 11-point Likert scale from 0=poor to 10-excellent
[b] 11-point Likert scale from 0=very light to 10=very deep

Study Conclusions: For Primary Endpoints:

- Eszopiclone 2mg had a significantly shorter sleep latency compared with placebo over the double-blind period; p=.0034. Eszopiclone 2mg had a significantly longer TST compared with placebo over the double-blind period; p=.0003.
- Eszopiclone 1mg had a significantly shorter sleep latency compared with placebo over the double-blind period; p=.012. Eszopiclone 1mg was not significantly different from placebo for TST across the double-blind period.

Study Conclusions: For Secondary Endpoints:

- Eszopiclone 2mg had significantly less WASO compared to placebo across the double-blind period; p≤.05. Eszopiclone 2mg was not significantly different from placebo in the number of awakenings per night. Eszopiclone 2mg had significantly higher quality (p=.0006) and better depth of sleep (p=.0015) compared with placebo over the double-blind period.
- Eszopiclone 1mg was not significantly different from placebo for WASO, number of awakenings, sleep quality, or sleep depth across the double-blind period.
- Eszopiclone 2mg significantly decreased patient reports of daytime alertness and a sense of physical well-being compared with placebo over the double-blind period. During the same interim, morning sleepiness and ability to function were marginally significant with eszopiclone 2mg compared with placebo. No significant differences between eszopiclone 1mg and placebo groups were observed for any of the daytime parameters across the double-blind period.
- Eszopiclone 2mg had significantly higher QOL compared with placebo on 5 of the 16 Q-LES-Q domains (physical health, mood, household activities, leisure time activities, and medication; p<.05). (data not shown). No significant differences between eszopiclone 1mg and placebo were observed for any of the Q-LES-Q dimensions.

Safety

- No AE were reported related to accidental falls, amnesia, or hallucinations

Quality Assessment: (Fair)

- Difficult to determine whether sleep apnea and/or limb movement disorders are present via clinical interviews in older adults.

Primary author is on the speakers' bureau for Sepracor. Two of the authors are full-time employees of Sepracor. The data were analyzed by Sepracor Inc. The paper was written by the authors with the assistance of Sepracor Inc.